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HIGH PRODUCTION VOLUME (HPV) CHEMICAL CHALLENGE PROGRAM

TEST PLAN

For The Trimellitate Category

Prepared by:

ExxonMobil Biomedical Sciences, Inc.

For The

**Phthalate Esters Panel, HPV Testing Group
of the American Chemistry Council**

**December 18, 2006
(Revision to Test Plan Dated December 13, 2001)**

THE PHTHALATE ESTERS PANEL

The American Chemistry Council, Phthalate Esters Panel sponsoring this test plan includes the following member companies:

Eastman Chemical Company
ExxonMobil Chemical Company
Sunoco Chemicals
Teknor Apex Company

TRIMELLITATE CATEGORY

CAS Number	CAS Number Description
3319-31-1	1,2,4-benzenetricarboxylic acid, tris (2-ethylhexyl) ester
27251-75-8	1,2,4-benzenetricarboxylic acid, triisooctyl ester
53894-23-8	1,2,4-benzenetricarboxylic acid, triisononyl ester
67989-23-5	1,2,4-benzenetricarboxylic acid, decyl octyl ester

PLAIN ENGLISH SUMMARY

The trimellitates category contains four U.S. HPV (High Production Volume) trimellitates. These substances are 1,2,4 benzenetricarboxylic acids with side chain esters ranging from C8-C10. Of these, the one most extensively tested, Tris-2(ethylhexyl) trimellitate (TOTM), has been shown to have a low order of toxicity. Existing toxicology data on these substances were supplemented with information on phthalate esters (1,2 benzenedicarboxylic acids) with side chains of similar length.

The American Chemistry Council, Phthalate Esters Panel, HPV Testing Group believes that there is a sufficient amount of information available on trimellitates to substantially characterize the human health effects and environmental fate and effects endpoints for the remaining members of this category under the HPV program. TOTM has been sponsored under the OECD (Organization for Economic Co-operation and Development) SIDS (Screening Information Data Set) HPV Program through ICCA. A full SIDS data set exists for TOTM and is being used to support the hazard assessment of the remaining trimellitates in this category. No additional toxicology tests are proposed for these materials.

EXECUTIVE SUMMARY

The American Chemistry Council, Phthalate Esters Panel, HPV (High Production Volume) Testing Group and its member companies hereby submit for review and public comment the test plan for the Trimellitate category under the U.S. Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program (Program). It is the intent of the Phthalate Esters Panel and its member companies to use existing data and scientific judgment/analyses to meet the requirements of the Screening Information Data Set (SIDS) for human health, environmental fate and effects, and physicochemical properties for this category.

This test plan addresses the 4 HPV trimellitates listed in Table 1. Trimellitates are produced by esterification of trimellitic anhydride (TMA) with various linear and branched alcohols in the presence of an acid catalyst to form 1,2,4 –benzenetricarboxylic acids. Because the side chains for all substances in this category are of similar carbon number (C8-C10) and structure, all four of the HPV substances were grouped into a single category.

Trimellitates are used predominantly as plasticizers for production of flexible PVC. Because of their relatively high molecular weight (>500 g/mole) and bulky structure, they have lower volatility and greater resistance to migration than the corresponding phthalate ester plasticizers. They are predominantly used in the manufacture of high temperature PVC cables (Wilson, 1996). Since these chemicals are produced in closed systems, there is essentially no occupational exposure to these substances except at the flexible PVC production facility. Usually, these substances have been already blended to the compound as plasticizer, so it is not expected that downstream users or consumers are directly exposed to trimellitates.

Testing Rationale:

Because of the similarity in chemical structure, the Panel believes that the toxicological properties of the substances in this category will be similar as well. Thus, the Panel considers that the data for the best tested member of this category, tris-2(ethylhexyl) trimellitate (TOTM), also represent the potential for human and environmental effects of the other members of this category. In addition, data on TOTM indicate that it is hydrolyzed very poorly in rodents to the di-2-ethylhexyl ester and a mono-2-ethylhexyl ester. Therefore, "read across" for trimellitates would consist of comparisons to the similar phthalate esters, which are also being sponsored by the Panel under the U.S. HPV program. Existing toxicology data on these substances were supplemented with information on phthalate esters (1,2 benzenedicarboxylic acids) with side chains of similar length (see test plan for phthalate esters category).

TOTM has been sponsored by Japan under the OECD SIDS HPV program. A review of the available data for TOTM (Table 2) indicates that all endpoints have been adequately addressed, and that TOTM exhibits a low order of toxicity. Further, a comparison of the relative toxicity of TOTM to its corresponding phthalate ester, di-ethylhexyl phthalate (DEHP), indicates that trimellitates are much less active than phthalate esters with side chains of similar length. Due to their higher molecular weight and bulky side chains, the remaining members of this category are expected to demonstrate a lower order of toxicity than TOTM. This is supported by a similar structural-activity relationship observed with phthalate ester compounds, i.e., the higher molecular weight phthalates (ester side chains $\geq$C7) are less active that the transitional phthalates (ester side chains C4-C6). Thus, the use of TOTM to represent the potential hazards of the other category members is a conservative position. No additional toxicity tests are proposed for this category.

TEST PLAN FOR THE TRIMELLITATE CATEGORY

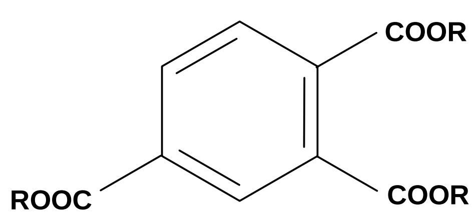
INTRODUCTION

The American Chemistry Council, Phthalate Esters Panel, HPV Testing Group and its member companies have committed voluntarily to develop screening level human health effects, environmental fate and effects, and physicochemical data for the trimellitates category under the U.S. Environmental Protection Agency's (EPA's) High Production Volume (HPV) Challenge Program.

This plan identifies CAS numbers used to characterize the SIDS endpoints for this category, identifies existing data of adequate quality for substances included in the category, and provides the Panel's rationale for utilizing the available SIDS data to characterize the potential hazards of all category members. The objective of this effort is to identify and adequately characterize the physicochemical properties along with human health, environmental fate and effects, to satisfy the EPA HPV program.

DESCRIPTION OF THE TRIMELLITATES CATEGORY

The trimellitates comprise a family of chemicals synthesized by esterifying trimellitic anhydride with alcohols with average carbon numbers ranging from approximately C7-C10, in the presence of an acid catalyst. The category includes the four trimellitates listed in Table 1. Trimellitates in this category are all 1,2,4-benzenetricarboxylic acids with side chain ester groups ranging from C8 to C10. The structural formula for trimellitates varies somewhat depending on the isomeric composition of the alcohols used in their manufacture. The specific alcohols used are 2-ethylhexanol (TOTM), iso-octyl alcohol (TIOTM), iso-nonyl alcohol (TINTM), and a mixture of linear and branched decyl (40%) and octyl (60%) alcohols (DOTM).



Trimellitates are colorless to slightly yellow liquids with high boiling points (> 250^{o}C) and low vapor pressures; these properties contribute to their high physical stability. They are readily soluble in most organic solvents and miscible with alcohol, ether and most oils, but essentially insoluble in water. Because of the similarity in structure as well as physicochemical properties, the trimellitates were grouped into a single category containing four substances with carboxylic side chain ester groups ranging from C8-C10.

DATA ADEQUACY REVIEW

Literature Search:

Literature searches were conducted by EMBSI Information Services on the environmental and mammalian toxicity endpoints for four trimellitates using the CAS numbers supplied by the Phthalate Esters Panel. A review of these substances was recently published (David *et al.*, 2001). Therefore, the search was conducted using the MEDLINE and TOXLINE databases and limited to studies published since 1995. The TSCATS database was searched for relevant unpublished studies on these chemicals. In addition, a complete SIDS information package on TOTM was kindly provided by Dainippon Ink & Chemicals, Japan, as part of it's OECD SIDS HPV submission. Standard handbooks and other reference material (CRC Handbook on Chemicals; IUCLID) were consulted for physicochemical properties. Information on manufacture and use was taken from EPA (1981) and Wilson (1996).

In addition, modeled data were entered into the robust summaries for all of the physical properties. There are a number of reasons for this approach:

- The EPA guidance (www.epa.gov/opptintr/chmrtk/robsumgd.htm) allows inclusion of calculated values in the robust summaries for physicochemical elements,
- The need for a complete set of physical property data in order to calculate environmental distribution, and
- Supplement measured physical properties for these trimellitates.

The physical properties were modeled using the SRI/EPA computer program EPI Suite^{TM}, (2000) a modeling package that includes a number of algorithms developed at or for the EPA. EPI Suite^{TM} is the program used and advocated by the EPA. Because the model is a structure-property model a specific discrete structure is required and EPI Suite^{TM} contains a CAS number database which contains the structures for the chemicals. For mixtures, a single representative structure is contained in the database and in this work, these surrogate chemical structures were accepted for further modeling. It should be remembered that the resultant physical properties are for a single structure not a mixture so the values are discrete numbers rather than ranges.

The existing data for environmental and mammalian toxicology endpoints were reviewed using the literature searches to identify the most relevant studies for each chemical in the group. A number of the listed individual chemicals had no relevant studies identified in the searches. For the listed chemicals for which there were relevant data, all studies were reviewed using the criteria outlined in the EPA's method for determining the adequacy of existing data for the HPV program and the ranking system proposed by Klimisch *et al.* (1997). A list of the most relevant studies that were available for environmental and mammalian health endpoints is presented in **Appendix 1.**

Studies that were chosen for robust summaries represented the best available data for each specific endpoint. Published studies from the general literature, as well as a number of unpublished company reports, were obtained and summarized. Some endpoints include multiple summaries in order to present a more complete data set.

TESTING RATIONALE

Overview:

The trimellitates category contains four U.S. HPV trimellitates. These substances are 1,2,4 benzenetricarboxylic acids with side chain esters ranging from C8-C10. Of these, the one most extensively tested, TOTM, will be used as a representative chemical to assess the potential environmental and health effects of the other trimellitate category members. A review of the available data for TOTM (Table 2) indicates that all endpoints have been adequately addressed, and that TOTM exhibits a low order of toxicity. Due to their higher molecular weight and bulky side chains, the remaining members of this category are expected to demonstrate a lower order of toxicity than TOTM. This is supported by a similar structural-activity relationship observed with phthalate ester compounds, i.e., the higher molecular weight phthalates (ester side chains ≥C7) are less active than the transitional phthalates (ester side chains C4-C6). Thus, the use of TOTM to represent the potential hazards of the other category members is a conservative position. No additional toxicity tests are proposed for this category.

Manufacturing and Use

Trimellitates are produced by esterification of trimellitic anhydride (TMA). The basic structure is an aromatic ring with side chains in the 1, 2 and 4 positions. Trimellitate plasticizers are based on alcohols with (average) carbon numbers in the range 7-9. The relatively high molecular weight and bulky structure of these molecules gives them low volatility and makes them relatively resistant to migration. Their main application is in high temperature PVC cables (Wilson, 1996).

Category Justification

The four trimellitates in the HPV category, tris-2(ethylhexyl) trimellitate (TOTM), tri-isooctyl trimellitate (TIOTM), tri-isononyl trimellitate (TINTM) and decyl,octyl – trimellitate (DOTM). The distinguishing feature of these substances is in the alcohol side chains. TOTM has side chains with a 2-ethylhexyl moiety, TIOTM has iso-octyl side chains, TINTM has isononyl side chains and DOTM has mixed decyl (40%) and octyl (60%) side chains. These molecules are of the same general structure, differing only in side chains, and the side chains themselves are very similar, containing carbon numbers ranging from C8 to C10. These molecules also have similar physical and chemical properties; in particular because of their high molecular weights and aliphatic character, they have very low vapor pressures and very low water solubilities. Because of the similarity in structure and physicochemical properties, the Panel believes that it is reasonable to consider this group of substances as a category and to rely on data for one representative member (TOTM) for all other representatives in this category.

Physicochemical Properties

Physicochemical properties for trimellitates are shown in Table 2A. The 2-ethylhexyl trimellitate ester (TOTM) is representative of this group of trimellitates as the other members are quite similar triesters of mellitic acid with C8 through C10 alcohols. TOTM has a melting point of -46°C and a boiling point of >300°C at 1 atmosphere (measured values are >300°C at reduced pressure). Vapor pressure measurements are only possible for TOTM at very high temperatures due to its low order of volatility.

Measured values are <1 Pa at 100°C and 13 Pa at 200°C; thus, the vapor pressure at 25°C is extrapolated to be < 0.01 Pa. The vapor pressure calculated for TOTM by EPI Suite™ is 7.8×10^{-10} Pa. The water solubility of TOTM is also quite low. A measured value of 4×10^{-4} mg/L is available. However, water solubility is difficult to measure at such low concentrations, particularly for esters with densities near that of water and which tend to form dispersions in water and for that reason, standard test methods tend to over-estimate water solubility. The EPI Suite™ calculated water solubility value for TOTM is 4.5×10^{-8} mg/L. The log of the octanol/water partition coefficient (log K_{ow}) for TOTM is calculated (EPI Suite™) as 11.6. Measured values of 5.94 and 4.35 are also available.

Structure-property modeling has been done using the EPI Suite™ program recommended by EPA.[1] This modeling has been used to estimate all of the required physicochemical parameters of all four of these HPV trimellitates. TOTM has a melting point below 0°C; it is expected that the other members of this group will have melting points below 0°C as well. Due to their high molecular weight, these trimellitates are expected to boil at a much higher temperature than TOTM and than the corresponding phthalate esters all of which boil at >300°C at atmospheric pressure. EPI Suite™ estimates boiling points >500°C for all four trimellitates. Thus, all boiling points are assuredly >300°C and measurement is not necessary.

For the phthalate esters, the EPI Suite™ model agrees well with measured values for the critical environmental fate properties of octanol-water partition coefficient, water solubility, and vapor pressure. By analogy with the phthalates and by EPI Suite™ calculations, these trimellitates are expected to be virtually water insoluble <1 part per billion) and non-volatile ($<10^{-9}$ Pa). Measured values on TOTM confirm the expected low water solubility and vapor pressures. The log K_{ow} values for all four trimellitates are calculated to be in the range of 11 to 13. The measured values reported for TOTM seem quite unlikely, since the measured value for the corresponding phthalate diester (DEHP) is 7.7 (which agrees well with the calculated value) and TOTM is expected to be much more hydrophobic due to the presence of a third ester group. Moreover, these measured values are more than 5 orders of magnitude lower than the calculated value.

The physical properties of vapor pressure and water solubility of the trimellitates are too low to measure accurately, as evidenced by the data for TOTM. Similarly the calculated log K_{ow} values are likely to be more accurate than laboratory measurements, due to high values beyond the range of applicability of the test methods. The water solubility is also so low as to make hydrolysis rate studies untenable. Thus, no further measurements of the physical properties of the trimellitates is necessary as the values calculated by QSAR models are likely to be as reliable or more reliable than the measured values.

Environmental Fate

There are data available on the degradability of TOTM, TIOTM, and TINTM. There are also data for a decyl,octyl,hexyl – trimellitate (DOHTM) that can be used as read-across to assess the biodegradability of DOTM. The measured abiotic degradation (hydrolysis) half-life of TOTM at pH 7 and 25°C is 17.5 days (0.05 year). The EPI Suite™ calculated

[1] US EPA (2000). The Use of Structure Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program, http://www.epa.gov/opptintr/chemrtk/sarfinl1.htm

hydrolysis half-life is 0.3 year. The atmospheric degradation half-life (hydroxyl radical attack) calculated by EPI Suite™ (AOP module) is 0.33 day. Measured biodegradability results for TOTM include a 28-day value range of 68 to 71% based on ^{14}C-TOTM loss in a shake flask test, a 28-day value of 47%, which increased to 61% on day 39, based on oxygen consumption (OECD 301F, manometric respirometry test), and a 28-day value of 4.2%, based on oxygen consumption, in the Japanese MITI test (OECD 301C, modified MITI test). It is likely that the low result in the MITI test is due to lack of bioavailability since that test has a relatively high solids content. Measured biodegradability results show that TIOTM biodegraded to an extent of 5.47% on day 28, based on oxygen consumption (OECD 301F, manometric respirometry test). Measured biodegradability results show that TINTM biodegraded to an extent of 4.2% on day 28, which increased to 4.5% on day 39, based on oxygen consumption (OECD 301F, manometric respirometry test). Measured biodegradability results show that DOHTM biodegraded to an extent of 34% on day 28, which increased to 56% on day 39, based on oxygen consumption (OECD 301F, manometric respirometry test).

By analogy with the phthalates, whose biodegradation has been well established, degradation of the trimellitates is expected to proceed through step-wise hydrolysis of the ester groups to free alcohol and mellitic acid. These metabolites, in turn, are known to be rapidly degraded. No further degradation testing is necessary.

The calculated environmental distribution of TOTM (Mackay level 1) indicates that negligible fractions of TOTM will partition to air or water, with the major fractions partitioning to soil (97.7%) and sediment (2.2%). Distribution as calculated using the Mackay level 3 model supports this partitioning with 99.3 % to soil and 0.7% to sediment using a default emission rate of 1000 kg/hr into each of the air, water, and soil compartments. Due to closely similar physical properties, exactly the same environmental distribution is calculated for the other trimellitates in this group. Environmental fate properties are shown in Table 2A.

Toxicokinetics and Metabolism

Absorption and metabolism were studied for TOTM administered in corn oil by gavage in a single dose of 100 mg/kg of body weight in 4 male SD rats. Urine and feces were collected over the following 144 hour period, after which animals were sacrificed and residual carcass levels determined. About 75% of the dose was excreted in the feces, 16% in the urine as metabolites and 1.9% was expired as $^{14}CO_2$. Radioactivity was mostly excreted in the feces as unchanged TOTM (85% of the fecal radioactivity), with 6% as isomers of the diester and 1% as the mono-2-ethylhexyl trimellitate (MEHT). Metabolites in the urine were identified as MEHT and metabolites of 2-ethylhexanol. Less than 0.6% of the dose remained in the tissues. Elimination of $^{14}CO_2$ was biphasic with half-lives of 4.3 and 31 hrs, and excretion of radioactivity in the urine was biphasic with half-lives of 3.4 hrs and 42 hrs. (Eastman Kodak Company, unpublished report 1984).

These data indicate that TOTM is poorly hydrolyzed and absorbed across the gastrointestinal tract. By comparison, numerous absorption and metabolism studies on DEHP indicate that DEHP is readily hydrolyzed in the gut prior to absorption, with ~50% of the DEHP dose absorbed by rodents following oral administration (Albro and

Lavenhar, 1989). Hydrolysis in the gut appears to be an obligatory step for systemic absorption of phthalate esters. Thus, the relatively poor hydrolysis and systemic absorption of TOTM may in part explain the observed lower toxicity of trimellitates as compared to phthalate esters.

Mammalian Toxicity Data

A summary of the available toxicity data on trimellitates is shown in Table 2C.

Acute Toxicity

TOTM exhibits very limited acute toxicity with an oral LD_{50} > 2 g/kg, a dermal LD_{50} > 20 ml/kg (approximately 20 g/kg), and an acute inhalation LC_{50} in the range of 0.23 to 2.64 mg/L (nominal). There is, in addition, an acute oral LD_{50} value for TINTM of > 10 g/kg. Although some of these data are from older studies that may not have been fully consistent with current guidelines, these results are consistent with those from studies of phthalate esters produced from similar alcohol feedstocks. These data indicate that acute toxicity is not a concern for molecules of this type. No additional acute toxicity testing is planned for this category.

Repeated Dose Toxicity

TOTM was tested for repeated dose toxicity in rats. Exposure was by dietary administration at levels of 0.2, 0.67, and 2.0%. There was no statistically significant difference of bodyweight between the control and TOTM treated groups of either sex. Female rats fed 2.0% TOTM consumed significantly less diet than the controls during first week of treatment after which their intakes increased but remained lower than those of the controls. In the males there were no statistically significant differences between the control and TOTM fed groups during the treatment period. In both sexes haemoglobin concentration of the rats given diet containing 0.67 or 2.0% TOTM were statistically significantly lower than the control. In both sexes the liver weights, and liver weights relative to bodyweight, were increased in the TOTM treated animals compared to the controls. These differences were small and not statistically significant in the 0.2% TOTM group. Analysis of serum from the males and females showed statistically significantly increased levels of albumin in the groups given 0.67 or 2.0% TOTM (104 to 108% of control). In the males there were statistically significantly higher cholesterol levels in the 0.67 and 2.0% TOTM groups (115 to 125% of control). Concentration of serum urea was statistically significantly increased in the male 2.0% TOTM group to the control value (115%). In the females there was also an isolated statistically significantly lower value for lipid concentration in the 0.2% TOTM group (83% of control). There was also evidence of increased metabolic enzymes and cholesterol. There were also some changes in blood parameters but these were inconsistent, and were judged to be without toxicological consequence. No pathologic abnormalities were detected in the majority of the animals. Two female rats fed 2.0% TOTM showed marginal reductions in cytoplasmic basophilia in the liver. Transmission electron microscopy showed that 2.0% TOTM exposure produced a slight increase in the numbers of peroxisomes which varied between cells. No difference was seen between the centrilobular and periportal areas. The NOAEL for repeated dose toxicity is considered to be 184 mg/kg/day (0.2%) and the LOAEL is considered 650 mg/kg/day (0.67%) for both sexes. A NOAEL of 1000 mg/kg/day was reported in an unpublished 28 day oral feeding study in rats (Japan

Ministry of Health & Welfare, 1996). Based on these data, no additional subchronic toxicity testing is planned for this category.

Mutagenicity

TOTM was not mutagenic in Salmonella and did not cause mutations in the HGPRT assay in CHO cells.

Additionally, there was no increase in unscheduled DNA synthesis in rat hepatocytes. TOTM induced neither structural chromosomal aberrations nor polyploidy in CHL/IU cells up to the limit concentration of 5.0 mg/ml, in the absence or presence of an exogenous metabolic activation system. In addition, a wide range of phthalate esters produced from similar C8-C10 alcohol feedstocks have been evaluated for both point mutations (Zeiger *et al.*, 1987; Barber *et al.*, 2000) and chromosomal aberrations (McKee, 2000) and have consistently been found to be inactive. Based on these data there is no need to conduct additional tests of trimellitates for point mutations or chromosomal aberrations.

Reproductive/Developmental Toxicity

TOTM was studied for oral toxicity in rats in an OECD preliminary reproduction toxicity screening test at doses of 0, 100, 300 and 1000 mg/kg/day. Histopathological examination of the testes revealed slight to moderate decreases in spermatocytes and spermatids in males of the 300 and 1000 mg/kg group. Decreases in spermatocytes as compared to control fell in the range of 10-19% with the 1000 mg/kg group and 5-16% with the 300 mg/kg group. Decreases in round and elongate spermatids ranged from 16-19% and 18-34% in the 1000 mg/kg group, respectively. With 300mg/kg, 13-15% decreases in round spermatids and 9-21% decreases in elongate spermatids were observed. No effects of TOTM were detected on general appearance, body weight, food consumption, autopsy findings, and weights of the reproductive organs of both sexes, or on histopathological examination of the ovary. Except for the effects in males observed on histopathological examination, no influence of TOTM was detected regarding reproductive ability, organ weights or histopathological appearance of the ovaries, delivery or maternal behavior of dams. No effects of TOTM were detected on viability, general appearance, body weight or autopsy findings of offspring. On the basis of these findings, the NOELs of TOTM for reproductive/developmental effects were considered to be 100 mg/kg/day for males, 1000 mg/kg/day for females, and 1000 mg/kg/day for offspring.

A comparison of TOTM to DEHP indicates that TOTM is less active than its diester analog. The LOAEL for DEHP-induced reproductive and developmental effects is 140 mg/kg/day and 750 mg/kg/day, respectively. In contrast, with TOTM, the reproductive LOAEL was 300 mg/kg/day (decreases in spermatocytes and spermatids) in males and the NOAEL for developmental effects was 1000 mg/kg/day.

Phthalate esters produced from similar C8-C10 alcohol feedstocks as used to produce trimellitates have also been extensively studied for potential reproductive and developmental effects. Phthalate esters with linear alkyl chains $\geq$C7 (High molecular weight phthalates), demonstrate neither reproductive nor developmental effects in rodents. Thus it is highly unlikely that the remaining trimellitates in this category will exhibit any reproductive or developmental effects. No further reproductive or developmental testing is proposed for this category.

Environmental Toxicity

A summary of the available toxicity data on trimellitates is shown in Table 2B. There are aquatic toxicity data available for TOTM in fish, daphnia, and algae. No acute toxic effects to fish (*Oryzias latipes*) were observed at the highest concentration tested, 100 mg/L. Similarly, no effects were observed in algae (*Selenastrum capricornutum*) at 100 mg/L (NOEC = 100 mg/L) and *Daphnia magna* at the highest concentration tested, 180 mg/L. It should be noted that all of these toxicity tests were conducted at concentrations many orders of magnitude higher than the true water solubility of TOTM through the use of a chemical dispersants. The calculated values for TOTM acute toxicity also predict no effects at the limit of water solubility. Chronic fish and daphnia exposure studies on TOTM also show no toxicity at and above its water solubility limit.

No measured aquatic toxicity data are available for the remaining members of this category. However, all of these are similar in structure to TOTM and to the higher phthalates and are expected to have the same characteristic aquatic toxicity, namely none. They are even less water soluble than the higher phthalates and like the higher phthalates, their solubility is too low to result in toxicity to aquatic organisms.

In addition, quantitative structure activity relationships (QSARs) are acceptable sources of ecotoxicity information for the evaluation for chemicals that belong to chemical classes with established QSARs.[2] Esters are such a class and the EPA's QSAR model "ECOSAR" may be relied upon to evaluate the potential aquatic toxicity of these trimellitate esters. No additional environmental testing is proposed for this category.

TEST PLAN SUMMARY

The American Chemistry Council Phthalate Esters Panel HPV Testing Group believes that there is a sufficient amount of information available on TOTM to substantially characterize the human health effects and environmental fate and effects endpoints for the remaining members of this category under the HPV program.

Physicochemical properties and environmental fate for all category members were calculated using appropriate QSAR models, and supplemented with measured data from the literature. Due to the poor solubility of these materials, the values calculated by QSAR models are likely to be as reliable as or more reliable than the measured data.

Mammalian toxicity data on TOTM is being used to characterize the potential hazards of the remaining category members. Sufficient SIDS data exists on TOTM to reliably assess acute toxicity, repeat dose toxicity, point mutations, chromosomal aberrations, and reproductive toxicity. The developmental effects of TOTM were indirectly measured in an OECD preliminary reproduction toxicity screening test. Extensive reproductive and developmental studies on phthalate esters were used as supportive information to characterize these endpoints.

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[2] US EPA (2000). The Use of Structure Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program, http://www.epa.gov/opptintr/chemrtk/sarfinl1.htm.

Both calculated and measured values for TOTM environmental toxicity endpoints predict no effects at the limit of water solubility. As the remaining trimellitates are even less water-soluble than TOTM, their solubility is too low to result in toxicity to aquatic organisms.

No additional toxicology tests are proposed for these materials.

Table 1. CAS Numbers and Descriptions

CAS Number	CAS Number Description	Acronym
3319-31-1	1,2,4-benzenetricarboxylic acid, tris (2-ethylhexyl) ester	TOTM
27251-75-8	1,2,4-benzenetricarboxylic acid, triisooctyl ester	TIOTM
53894-23-8	1,2,4-benzenetricarboxylic acid, triisononyl ester	TINTM
67989-23-5	1,2,4-benzenetricarboxylic acid, decyl octyl ester	DOTM

Table 2. Category Analysis Table: Physicochemical, Environmental Fate, Mammalian and Environmental Toxicology, and Biodegradation Data Summary for Trimellitates

A. Physicochemical Properties and Physical Degradation Half-Life Data for Trimellitates

(R) Carbon Chain Length	CAS Number	Chemical Name	MP *[c] (°C)	BP **[c] (°C)	VP [c] (hPa@25°C)	PC [c] (log Pow)	Water Solubility [c] (mg/L @25°C)	Photodeg Half-life [c] (days)	Hydrolysis Half-life [c] (yrs)
C8	3319-31-1	Tri 2-ethylhexyl trimellitate ester (TOTM)	-46 (m)	541 c	7.8E-8 c	11.59	4.5E-08	0.33	0.3
C8	27251-75-8	Triisooctyl trimellitate ester (TIOTM)	-46 (ra)	541 c	5.3E-11 c	11.59	4.5E-08	0.35	0.4
C9	53894-23-8	Triisononyl trimellitate ester (TINTM)	-46 (ra)	575 c	3.17E-12 c	13.06	1.3E-09	0.31	0.9
C8,C10	67989-23-5	Decyl, octyl trimellitate ester (DOTM)	-46 (ra)	585 c	1.4E-12 c	12.79	2.8E-09	0.32	1.0

(c) calculated data from EPI Suite™ (2000) (m) measured data (ra) read-across data
* All of these trimellitates are liquids at zero degrees C. Modeled data do not accurately reflect melting points for these substances.
** Measured boiling points were determined to be >300°C at 0.66 kPa.

B. Mackay Partitioning Data for Trimellitates

(R) Carbon Chain Length	CAS Number	Chemical Name	Mackay Level I Transport (%)						Mackay Level III Transport (%)			
			Soil	Sediment	Suspended Sediment	Air	Water	Biota	Soil	Sediment	Air	Water
C8	3319-31-1	Tri 2-ethylhexyl trimellitate ester (TOTM)	97.7	2.2	0.1	<0.1	<0.1	<0.1	99.3	0.7	<0.1	<0.1
C8	27251-75-8	Triisooctyl trimellitate ester (TIOTM)	97.7	2.2	0.1	<0.1	<0.1	<0.1	99.3	0.7	<0.1	<0.1
C9	53894-23-8	Triisononyl trimellitate ester (TINTM)	97.7	2.2	0.1	<0.1	<0.1	<0.1	99.3	0.7	<0.1	<0.1
C8,C10	67989-23-5	Decyl, octyl trimellitate ester (DOTM)	97.7	2.2	0.1	<0.1	<0.1	<0.1	99.3	0.7	<0.1	<0.1

C. Toxicology and Biodegradation Data for Trimellitates

(R) Carbon Chain Length	CAS Number	Chemical Name	Acute Oral LD50	Acute Dermal LD50	Acute Inhalation LC50	Repeated Dose Toxicity	Genetic Toxicity (Ames)	Genetic Toxicity (Chrom. Abs.)	Reproductive Toxicity	Developmental Toxicity / Teratogenicity	Acute Fish (A) mg/L	Acute Daphnia (B) mg/L	Alga Toxicity (C) mg/L	Percent Biodegradation (28-day)
C8	3319-31-1	Tri 2-ethylhexyl trimellitate Ester (TOTM)	>3.2 g/kg (rat, mouse) (m)	>20 ml/kg (guinea pig) >2.0 ml/kg (rabbit) (m)	>0.23 <2.64 mg/L (rat, nominal) (m)	NOAEL 184 mg/kg/day; LOAEL 654 mg/kg/day (rat, dietary) (m)	Negative (m)	Negative (CHL/IU cells) (m)	100 mg/kg/day for males, 1000 mg/kg/day for females, and 1000 mg/kg/day for offspring (rat, dietary) (m)	NOAEL (rat, oral) 1000 mg/kg/day (1) (m)	No mortality at saturation (m)	No immobility at saturation (m)	No effects at saturation (m)	68-71 (2) 4 (3) 47 (4) (m)
C8	27251-75-8	Triisooctyl trimellitate Ester (TIOTM)	>3.2 g/kg (rat, mouse) (ra)	>20 ml/kg (guinea pig) >2.0 ml/kg (rabbit) (ra)	>0.23 <2.64 mg/L (rat, nominal) (ra)	NOAEL 184 mg/kg/day; LOAEL 654 mg/kg/day (rat, dietary) (ra)	Negative (ra)	Negative (CHL/IU cells) (ra)	100 mg/kg/day for males, 1000 mg/kg/day for females, and 1000 mg/kg/day for offspring (rat, dietary) (ra)	NOAEL (rat, oral) 1000 mg/kg/day (1) (ra)	No mortality at saturation (ra)	No immobility at saturation (ra)	No effects at saturation (ra)	5 (4) (m)
C9	53894-23-8	Triisononyl trimellitate Ester (TINTM)	>10 g/kg (rat) (m)	>20 ml/kg (guinea pig) >2.0 ml/kg (rabbit) (ra)	>0.23 <2.64 mg/L (rat, nominal) (ra)	NOAEL 184 mg/kg/day; LOAEL 654 mg/kg/day (rat, dietary) (ra)	Negative (ra)	Negative (CHL/IU cells) (ra)	100 mg/kg/day for males, 1000 mg/kg/day for females, and 1000 mg/kg/day for offspring (rat, dietary) (ra)	NOAEL (rat, oral) 1000 mg/kg/day (1) (ra)	No mortality at saturation (ra)	No immobility at saturation (ra)	No effects at saturation (ra)	4 (4) (m)
C8, C10	67989-23-5	Decyl, octyl trimellitate Ester (DOTM)	>3.2 g/kg (rat, mouse) (ra)	>20 ml/kg (guinea pig) >2.0 ml/kg (rabbit) (ra)	>0.23 <2.64 mg/L (rat, nominal) (ra)	NOAEL 184 mg/kg/day; LOAEL 654 mg/kg/day (rat, dietary) (ra)	Negative (ra)	Negative (CHL/IU cells) (ra)	100 mg/kg/day for males, 1000 mg/kg/day for females, and 1000 mg/kg/day for offspring (rat, dietary) (ra)	NOAEL (rat, oral) 1000 mg/kg/day (1) (ra)	No mortality at saturation (ra)	No immobility at saturation (ra)	No effects at saturation (ra)	34 (5) (m)

Footnotes: A) Japanese Medaka (*Oryzias latipes*), 96 hr LC50
B) *Daphnia magna*, 48-hr EC50

C) *Selenastrum capricornutum* (renamed *Psuedokirchneriella subcapitata*), 72-hr EC50
(m) measured data
(ra) read-across data (from TOTM)
(1) OECD Preliminary reproduction toxicity screening test; indirect measure of developmental effects
(2) Acclimated biodegradation by Shake Flask method
(3) Ready biodegradation by MITI method (OECD 301C)
(4) Ready biodegradation by manometric respirometry method (OECD 301F)
(5) Read-across ready biodegradation by manometric respirometry method (OECD 301F) using a hexyl-octyl-decyl trimellitate ester

References*

*The list of references is not a comprehensive bibliography of all of the trimellitate literature, merely a series of papers that illustrate key points made in the text. The information in these papers also supplements the robust summaries developed for toxicology studies of listed substances in tests addressing specific SIDS endpoints.

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Appendix 1: Literature Search

3319-31-1 1,2,4-benzenetricarboxylic acid, tris (2-ethylhexyl)ester

Reviews

Japan dossier and robust summary for tris(2-ethylhexyl) benzene-1,2,4-tricarboxylate. (DRAFT unpublished report, 2001).

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ExxonMobil Biomedical Sciences, Inc. (2005). Ready Biodegradability: OECD 301F Manometric Respirometry Test. Study No. 0533179. Unpublished report.

53894-23-8   1,2,4-benzenetricarboxylic acid, triisononyl ester

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ExxonMobil Biomedical Sciences, Inc. (2005). Ready Biodegradability: OECD 301F Manometric Respirometry Test. Study No. 0533179. Unpublished report.

67989-23-5   1,2,4-benzenetricarboxylic acid, decyl octyl ester

ExxonMobil Biomedical Sciences, Inc. (2005). Ready Biodegradability: OECD 301F Manometric Respirometry Test. Study No. 0533179. Unpublished report.